530 Rec'd PCT/PTO 28 JUN 2001

FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)
PA-9847	To be assigned 09/869630

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB99/04395	December 23, 1999	December 30, 1998

TITLE OF INVENTION
NMR Spectroscopy Method

APPLICANT(S) FOR DO/EO/US
Peter Knox and Neil Cook

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

copy of this transmittal letter for charging purposes
copy of the International Application as published by the International Bureau
return postcard

ICATION NO. (IF KNOWN, SEE 37 CFR	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/869630 To be Assigned	PCT/GB99/04395	PA-9847

The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1000.00	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$860.00	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$710.00	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$690.00	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =		$860.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	9 - 20 =	0	x $18.00	$0.00
Independent claims	1 - 3 =	0	x $80.00	$0.00
Multiple Dependent Claims **(check if applicable)**.			☐	$0.00
TOTAL OF ABOVE CALCULATIONS =				$860.00
☐ Applicant claims small entity status. (See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				$0.00
SUBTOTAL =				$860.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$0.00
TOTAL NATIONAL FEE =				$860.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				$0.00
TOTAL FEES ENCLOSED =				$860.00
			Amount to be: refunded	$
			charged	$

a. ☐ A check in the amount of _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **500-588** in the amount of **$860.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **500-588** A duplicate copy of this sheet is enclosed.

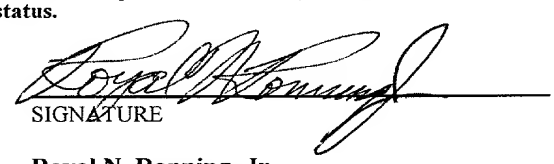
d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Royal N. Ronning, Jr.
Amersham Pharmacia Biotech, Inc.
800 Centennial Avenue
Piscataway, New Jersey 08855

(732) 457-8423



SIGNATURE

Royal N. Ronning, Jr.
NAME

32,529
REGISTRATION NUMBER

June 28, 2001
DATE

PA-9847

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	P. Knox, et al.	Group Art Unit:	To be assigned
Serial Number:	To be assigned	Examiner:	To be assigned
Filing Date:	June 28, 2001		
Title:	NMR Spectroscopy Method		

FIRST PRELIMINARY AMENDMENT

Honorable Assistant Commissioner of Patents
Box New Patent Application
Washington, D.C. 20231

Sir:

Please consider the following amendments and remarks in connection with the prosecution of the captioned application, which is a filing under 35 U.S.C. § 371 and claims priority to international application number PCT/GB99/04395 filed December 23, 1999 and to application number 9828853.3 filed in Great Britain on December 30, 1998.

In the Claims

Please amend page 6, line 1 as follows:

[CLAIMS]

What is claimed is:

Please amend claim 5 as follows:

5. (once amended) The method of [any of claims 1 to 4]claim 1 wherein the biological molecule is a peptide or a protein.

Please amend claim 6 as follows:

6. (once amended) The method of [any of claims 1 to 5]claim 1 wherein the hyperpolarised ^{129}Xe is enriched at a level of 40% or more.

Please amend claim 7 as follows:

7. (once amended) The method of [any of claims 1 to 6]claim 1 wherein the degree of hyperpolarisation is 8% or more.

Please amend claim 8 as follows:

8. (once amended) The method of [any of claims 1 to 7]claim 1 which is performed in a solution wherein the solvent has a viscosity in the range of 700 to 1500 mPs.

Please amend claim 9 as follows:

9. (once amended) The method of [any of claims 1 to 8]claim 1 wherein the pressure of the xenon gas is at least 5 bar.

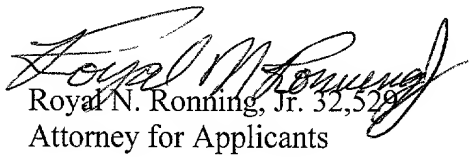
Remarks

Claims 1-9 are pending in the instant application. Applicants have amended claims 5, 6, 7, 8, and 9 to more fully conform with U.S. practice and to delete multiple dependencies. A version of the claims marked up to show the amendments, as well as a clean version of the claims encompassing the amendments, is attached hereto.

Applicants respectfully assert that all amendments are fairly based on the specification, and respectfully request their entry.

Applicants believe that the claims, as amended, are in allowable form, and earnestly solicit the allowance of claims 1-9.

Respectfully submitted,



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Claims (marked-up version showing amendment(s))

[CLAIMS]

What is claimed is:

5. (once amended) The method of [any of claims 1 to 4]claim 1 wherein the biological molecule is a peptide or a protein.

6. (once amended) The method of [any of claims 1 to 5]claim 1 wherein the hyperpolarised ^{129}Xe is enriched at a level of 40% or more.

7. (once amended) The method of [any of claims 1 to 6]claim 1 wherein the degree of hyperpolarisation is 8% or more.

8. (once amended) The method of [any of claims 1 to 7]claim 1 which is performed in a solution wherein the solvent has a viscosity in the range of 700 to 1500 mPs.

9. (once amended) The method of [any of claims 1 to 8]claim 1 wherein the pressure of the xenon gas is at least 5 bar.

Claims (clean version encompassing amendments)

What is claimed is:

1. An *in vitro* method which comprises labelling a biological molecule with hyperpolarised ^{129}Xe, and observing a magnetic resonance (NMR) spectrum and/or NMR image of the hyperpolarised ^{129}Xe in the environment of the biological molecule.

2. The method of claim 1 wherein the biological molecule is an assay reagent taking part in an assay method.

3. The method of claim 2 wherein the assay is a competition assay or an immunoassay.

4. The method of claim 2 wherein the assay is a hybridisation assay or a binding assay.

5. (once amended) The method of claim 1 wherein the biological molecule is a peptide or a protein.

6. (once amended) The method of claim 1 wherein the hyperpolarised ^{129}Xe is enriched at a level of 40% or more.

7. (once amended) The method of claim 1 wherein the degree of hyperpolarisation is 8% or more.

8. (once amended) The method of claim 1 which is performed in a solution wherein the solvent has a viscosity in the range of 700 to 1500 mPs.

9. (once amended) The method of claim 1 wherein the pressure of the xenon gas is at least 5 bar.

NMR SPECTROSCOPY METHOD

This invention is concerned with nuclear magnetic resonance (NMR) spectroscopy and/or NMR imaging. The technique involves observing the spectrum/image of a NMR active nuclear species *in vitro* in order to obtain information about the environment in which the species is present. The spectra of NMR active nuclei vary depending on their environment, and this is reported in the literature (PNAS, 93,12932-6, 1996).

Noble gases having non-zero nuclear spin can be hyperpolarised, i.e. have their polarisation enhanced over the equilibrium polarisation, e.g. by the use of circularly polarised light. Preferred techniques for hyperpolarisation include spin exchange with an optically pumped alkali metal vapour and metastability exchange. Noble gases to which this technique can be applied include ^{3}He and ^{129}Xe. As described by M S Albert *et al* in US Patent 5,545,396, the technique can be used to prepare hyperpolarised noble gases that can be administered by inhalation for magnetic resonance imaging of the human body.

Xenon is chemically inert and has hydrophobic properties, and is capable of being weakly bound by hydrophobic regions of biological molecules (PNAS, 78, No 8, 4946-9, August 1981; Abstracts of the 11th Annual Meeting of the Society for Magnetic Resonance in Medicine (1992) page 2104). Thus it is possible to "label" biological molecules with xenon.

This invention concerns the method of labelling biological molecules with hyperpolarised ^{129}Xe. All macromolecules have a number of discrete hydrophobic and hydrophilic sites. Xenon will bind by hydrophobic interactions to hydrophobic sites with different affinity. The xenon labels the biological compound by becoming weakly bound to it, e.g. at specific hydrophobic sites on a surface of or within a cavity of a protein or other macromolecule.

The NMR sensitivity of hyperpolarised xenon is highly increased compared to non-hyperpolarised xenon. Another advantage of the present invention is the reversible and non-destructive nature of the bond between the xenon and the biological molecule. A further advantage is that the forming of the "bond" and subsequent measurement may be repeated if

needed. In addition, since xenon is a gas (condensation temperature of -106°C), it and may easily and rapidly be separated from the biological molecule if necessary. Moreover, xenon is essential chemically inert and will not adversely effect the biological molecule.

One embodiment of the invention thus provides an *in vitro* method which comprises labelling a biological molecule with hyperpolarised xenon, and observing a magnetic resonance spectrum and/or image of the hyperpolarised xenon in the environment of the biological molecule. The spectrum/image provides information about the environment(s) at which atoms of xenon are bound to the biological molecule. Any conformational change of the biological molecule resulting e.g. from the binding (or the disappearance) of a ligand (e.g. a lipid, carbohydrate, peptide, polypeptide, nucleic acid or any sort of drug) or cleavage by an enzyme, will cause an alteration in the xenon NMR spectrum. Each hydrophobic site in the biological molecule may give rise to a specific and characteristic NMR shift.

A further embodiment of the present invention is to take NMR "fingerprint(s)" of a known biological molecule. These fingerprints can subsequently be used to identify unknowns by direct comparison in a manner similar to infra-red spectroscopy.

A biological molecule as defined by the present invention is a monomeric or polymeric molecule that is present in biological systems or that is artificially introduced and is biologically active in such systems. Biological molecules include lipids, sugars and polysaccharides, nucleic acids (DNA, RNA), nucleosides, oligonucleosides, polynucleosides, nucleotides, oligonucleotides, polynucleotides, enzymes, vitamins and particularly peptides, polypeptides and proteins.

In one preferred embodiment of the invention, the labelled biological molecule is an assay reagent taking part in an assay method and wherein the assay reagent is labelled with hyperpolarised xenon. The labelling of the biological molecule with hyperpolarised xenon may be performed before, during or after performance of the assay.

An assay method according to the present invention is a test involving a reaction of one or more biological molecules. The assays include for example competition assays (e.g. receptor-

ligand antagonism, enzyme-substrate inhibitors, protein-protein interaction inhibitors), binding assays (e.g. receptor-ligand agonism, enzyme-substrate reactions, protein-protein interactions), immunoassays (e.g. for specific analytes), hybridisation assays (e.g. nuclease assays, mutation analysis, mRNA and DNA detection), test involving cells, organs and/or whole organisms. These tests may involve e.g. one or more lipids, saccharides, polynucleotides, oligonucleotides, nucleotides, peptides or proteins. Assays include binding studies performed on eukaryotic and prokaryotic microorganisms; binding studies performed on tissue *in vitro*; and binding studies in which an assay reagent is administered *in vivo* and an excretion product (e.g. urine, faeces, or breath) analysed by NMR *in vitro*.

By observing a change with time using NMR, the progress of a reaction can be followed during the course of an assay. Assays performed *in vitro* may conveniently be in multiwell plates, with either an assay reagent in the wells of the plate being labelled with hyperpolarised xenon, or a reagent being so labelled in bulk prior to being dispensed into individual wells of the plate.

Generally the biological molecule is present in a liquid medium into which the xenon is introduced as a gas. This may be achieved e.g. by bubbling it through the fluid or by contact with the biological molecule as a solid. Alternatively the xenon is introduced as a solution in a solvent, which is compatible with the biological molecule (e.g. in a lipophilic solvent such as a lipid or a fluorocarbon solvent).

The liquid medium used according to one embodiment of the present invention may be deuterated water, deuterated buffers or solvents, e.g. lipophilic solvents which may contain lipid bicelles, lipid vesicles, liposomes, cryptophanes and/or cyclodextrins.

^{129}Xe has a natural abundance of 26.4%. The xenon used for this invention may be either the naturally occurring material or one artificially enriched in ^{129}Xe. A preferred degree of enrichment ^{129}Xe is 40 % or more. A more preferred degree is 50 % or more and an even more preferred degree is 75 % or more. A particularly preferred degree of enrichment is 90 % or more. Bulk supplies of xenon enriched in ^{129}Xe and hyperpolarised to a high degree are now available commercially and have a half life long enough to permit transport over substantial

distances. While the half life of hyperpolarised ^{129}Xe in the biological environments contemplated in this invention will be lower, it is expected to be amply sufficient to permit the desired spectra to be obtained. A preferred degree of hyperpolarisation is 8 % or more. A more preferred hyperpolarisation degree is 20 % or more and an even more preferred degree is 30 % or more. Ideally, the degree will approach 100 %.

In one embodiment of the invention, the temperature at the time xenon is added is above the temperature at which the biological molecule is frozen, but below the temperature at which the biological molecule may be denatured. Alternatively, xenon may be added to the frozen biological molecule, followed by thawing. However, the right temperature to achieve the optimal function of the biological molecule should also be considered.

In one embodiment of the invention, the solution is kept as low as possible in order to slow down the exchange between the bound xenon and free xenon, without broadening the NMR signals too much.

In a further embodiment of the invention, the solution is made viscous due to the use of one viscous solvent or the use of a suitable combination of solvents. The viscosity of the solvent is preferably within the range of 500 mPs to 5000 mPs, more preferably within the range of 700 mPs to 1500 mPs.

In one embodiment of the invention, the pressure of xenon is as high as possible, preferably higher than 5 $x10^5$ N/m^2 (5 bar), more preferably higher than 5 x 10^6 N/m^2 (50 bar), even more preferably higher than 1 $x10^7$ N/m^2 (100 bar) and particularly higher than $2x10^7$ N/m^2 (200 bar). However, the pressure must never be so high that the biological molecule will be adversely effected.

The invention is illustrated with reference to the following non-limiting Example.

Hyperpolarised ^{129}Xe is generated by optical pumping as described by B.Driehuys et al., Appl.Phys.Lett. 69 (12), 1996. The Isotopic composition of the gas is 80% ^{129}Xe and 0.25% ^{131}Xe (the rest non-magnetic isotopes of Xe). The degree of polarisation is estimated to be 10%.

Lyzozyme (28 mg) is dissolved in a mixture of D_2O and methanol-d_4 (40:60) (3 ml) in a heavy-walled 10 mm NMR-tube. This mixture is subjected to four freeze-pump-thaw cycles of degassing. The tube is then connected to the outlet of the polariser and frozen in liquid nitrogen. The hyperpolarized gas is generated and collected on a cold finger at liquid nitrogen temperature in a holding field of 200 mT over a period of 15 minutes which is estimated to give a volume of 50 ml of Xe at NTP. A narrow Dewar vessel with liquid nitrogen is placed in a magnet with a field strength of 0.3 T. The collected xenon is thawed and then refrozen in the NMR-tube in the 0.3 T magnet. The sample tube is flame-sealed and the frozen sample is moved to the fringe field of the magnet of an NMR-spectrometer. The NMR-spectrometer sample space is kept at a temperature of 293 K. The sample is removed from the transport magnet and thawed by heating with the hand (protected from the cold) while standing as close to the NMR-magnet as possible. When the sample starts to thaw it is shaken vigorously and inserted into the spectrometer. A ^{129}Xe spectrum is recorded and apart from the large peak due to the bulk xenon, a small peak, with a line width of 160 Hz, due to bound xenon can be observed at -158 ppm relative to bulk xenon.

CLAIMS

1. An *in vitro* method which comprises labelling a biological molecule with hyperpolarised ^{129}Xe, and observing a magnetic resonance (NMR) spectrum and/or NMR image of the hyperpolarised ^{129}Xe in the environment of the biological molecule.

2. The method of claim 1 wherein the biological molecule is an assay reagent taking part in an assay method.

3. The method of claim 2 wherein the assay is a competition assay or an immunoassay.

4. The method of claim 2 wherein the assay is a hybridisation assay or a binding assay.

5. The method of any of claims 1 to 4 wherein the biological molecule is a peptide or a protein.

6. The method of any of claims 1 to 5 wherein the hyperpolarised ^{129}Xe is enriched at a level of 40 % or more.

7. The method of any of claims 1 to 6 wherein the degree of hyperpolarisation is 8 % or more.

8. The method of any of claims 1 to 7 which is performed in a solution wherein the solvent has a viscosity in the range of 700 to 1500 mPs.

9. The method of any of claims 1 to 8 wherein the pressure of the xenon gas is at least 5 bar.

Please type a plus sign (+) inside this box → [+]

PTO/SB/01 (12-97)
Approved for use through 9/30/00. OMB 0651-0032
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing **OR** ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	PA-9847
First Named Inventor	Knox
COMPLETE IF KNOWN	
Application Number	09 /869,630
Filing Date	28-Jun-2001
Group Art Unit	To be assigned
Examiner Name	To be assigned

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NMR Spectroscopy Method

(Title of the Invention)

the specification of which
☐ is attached hereto
OR
☒ was filed on (MM/DD/YYYY) 06/28/2001 as United States Application Number or PCT International Application Number 09/869,630 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
9828853.3	Great Britain	12/30/1998	☐	☐	☒
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below

Application Number(s)	Filing Date (MM/DD/YYYY)

☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

Please type a plus sign (+) inside this box → [+]

PTO/SB/01 (12-97)
Approved for use through 9/30/00 OMB 0651-0032
Patent and Trademark Office; U S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*
PCT/GB99/04395	12/23/1999	

☐ Additional U S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to tra
and Trademark Office connected therewith: ☒ Customer Number 22840 → Place Customer Bar Code 22840
OR
☐ Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number

PATENT TRADEMARK OFFICE

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto

Direct all correspondence to: ☒ Customer Number or Bar Code Label 22840 OR ☐ Correspondence address below

Name					
Address					
Address					
City		State		ZIP	
Country		Telephone		Fax	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Peter	Knox

Inventor's Signature	Peter Knox					Date	30 7 01
Residence: City		State		Country	GB	Citizenship	GB
Post Office Address	"Choppings", 34 Kings Road, Buckinghamshire						
Post Office Address	Chalfont St. Giles, Great Britain HP8 4HS						
City		State		ZIP		Country	

☒ Additional inventors are being named on the 1 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

Please type a plus sign (+) inside this box → [+]

PTO/SB/02A (3-97)
Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 1 of 1

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
Neil			Cook				
Inventor's Signature	N. Cook					**Date**	20/8/01
Residence: City	Princeton	**State**	NJ	**Country**	USA	**Citizenship**	GB
Post Office Address	Amersham Pharmacia Biotech Inc, 800 Centennial Avenue						
Post Office Address	Piscataway, NJ 08855-1327, USA NJ						
City		**State**		**ZIP**		**Country**	

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
Post Office Address							
City		**State**		**ZIP**		**Country**	

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
Post Office Address							
City		**State**		**ZIP**		**Country**	

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